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Rigel Pharmaceuticals, Inc.
Bozicevic, Field & Francis LLP
1900 University Ave, Suite 200
East Palo Alto, CA 94303

EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/293,670	FISHER ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/16/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after the decision of the Board mailed on July 21, 2010 affirming the rejections. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/16/10 has been entered.

Election/Restrictions

Applicant's election with traverse of the species a) exocytic inducer, b) ionomycin, and c) a retroviral vector in the reply filed on 11/24/10 is acknowledged. The traversal is on the ground(s) that as stated in the MPEP §803, if search and examination of an entire application can be made without serious burden, the examiner must examine the entire application on the merits, even though the entire application includes claims to independent or distinct inventions. It is the Applicants' position that it would not be unduly burdensome to perform a search on all of the claims together in the present application.

Upon reconsideration of the species election/restriction and applicants' arguments, the restriction is withdrawn.

Status of Claims

Claims 37-44 are pending and under examination in the application.

Claim Rejections - 35 USC § 112-Necessitated by Amendments

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter Rejection

Claim 37 is drawn to a method of screening, comprising: introducing a library of at least 10^3 vectors encoding different candidate agents into a population of mammalian cells grown in vitro; subjecting the population of cells to a physiological signal that stimulates a phenotype in cells of the same type in the absence of the candidate bioactive agents; sorting the individual cells in the population on the basis of at least three optical properties by fluorescent activated cell sorting (FACS), identifying a cell having a phenotype that is altered relative to other cells in the population; and sequencing the nucleic acid encoding said candidate agent in said cell that has an altered phenotype, thereby identifying said candidate agent in said cell.

Claim 37 in its entirety (as a unit) is not supported in the as-filed specification.

Applicants point support for claim 37 in general as found in the specification at page 3, line 36 to page 4, line 5 which discloses:

> In accordance with the objects outlined above, the present invention provides methods for screening bioactive agents for the ability to alter or modulate alterations in cellular phenotypes. The methods generally comprise combining at least one candidate bioactive agent and a population of cells, sorting the cells in a FACS machine by separating the cells on the basis of at least three, four or five cellular parameters. The candidate agents can be part of a molecular library comprising fusion nucleic acids encoding the candidate bioactive agents.

In reply, the above-cited section does not support claim 37 in its entirety (i.e., as a unit). It is not clear as to applicants' reference to the support for claim 37 **in general**. Cf. with the claims of the parent issued patent US

6,897,031('031 patent) which finds support in its entirety in specification at e.g., col. 2, lines 22-35. Thus, the present claim is also not supported in the parent application now issued '031 patent.

Applicants cite disparate sections of the specification to provide support for individual method steps or components recited in the general support of claim 37, for example:

1. **Mammalian cells grown in vitro:**

Applicants rely at page 10, line 20 of the specification for mammalian cells; for 10^3 library at page 10, line 9 and page 10, lines 10-12 for "*in vitro*" mammalian growth.

The specification at page 10, lines 10-12 recites:

> By a "population of cells" or "library of cells" or "plurality of cells" herein is meant at least two cells, with at least about 10^3 being preferred, at least about 10^6 being particularly preferred, and at least about 10^8 to 10^9 being especially preferred. The population or sample can contain a mixture of different cell types from either primary or secondary cultures although samples containing only a single cell type are preferred, for example, the sample can be from a cell line, particularly tumor cell lines (particularly when as outlined below. The cells may be any cell phase, either synchronously or not, including M, G1, S, and G2. In a preferred embodiment,

> cells that are replicating or proliferating are used; this may allow the use of retroviral vectors for the introduction of candidate bioactive agents. Alternatively, non-replicating cells may be used, and other vectors (such as adenovirus and lentivirus vectors) can be used. In addition, although not required, the cells are compatible with dyes and antibodies.

There is nothing in the above cited section that recites for mammalian cells grown *in vitro*. The at least 10^3 refers to a **library of cells** and not to a library of **10^3 vectors encoding different candidate agents.** Throughout the specification reference for 10^3 is made for cells. Not a single, express positive reference is made in the instant or parent application 09/062330 (now USP 6,897,031patent) that the vectors are 10^3 library and encoding 10^3 different candidate agents. [Please see Example 2 which recites a single vector encoding a single agent.]

2. **Physiological signal-** page 9, lines 36-37 and page 34, line 5 which states:

> In another example, the measurements of cell cycle regulation are determined wherein the condition or environment of the populations of cells differs from one another. For example, the cells may be evaluated in the presence or absence of physiological signals, for example hormones, antibodies, peptides, antigens, cytokines, growth factors, action potentials, pharmacological agents (i.e. chemotherapeutics, etc.), or other cells (i.e. cell-cell contacts). In another example, the measurements of cell

> cycle regulation are determined at different stages of the cell cycle process. In yet another example, the measurements of cell cycle regulation are taken wherein the conditions are the same, and the alterations are between one cell or cell population and another cell or cell population.

In reply, the full text is cited above rather than the text quoted by applicants which had been taken out of context. As such step 2 of the claim recites "**subjecting** the population of cells to a physiological signal that stimulates a phenotype in cells of the same type in the absence of the candidate bioactive agents". The specification above recites **evaluating** the cells in the presence or absence of physiological signals and not of the candidate bioactive agents. Page 34, line 5 below of the specification presents the same concept.

> For example, the **cells may be evaluated in the presence or absence of physiological signals**, such as **exocytic** inducers (i.e., Ca**, ionomycin, etc.), hormones, antibodies, peptides, antigens, cytokines, growth factors, action potentials, or other cells (i.e. cell-cell contacts). In another example, **the measurements of exocytosis** are determined at different stages of the exocytic process. In yet another example, the measurements of exocytosis are taken wherein the conditions are the same, and the alterations are between one cell or cell population and another cell or cell population. (Emphasis added.)

3. At **least three optical properties** - page 4, line 3 which recites:

> The methods generally comprise combining at least one candidate bioactive agent and a population of cells, sorting the cells in a FACS machine by, separating the cells on the basis of at least three, four or five **cellular parameters**. (Emphasis added.)

In reply, reference is made to at least three cellular parameters but not to the claimed at least three optical properties as in claim 37.

The specific optical properties are alleged to find support at page 34, lines 30 and 37:

> In a preferred embodiment, changes in light scattering are assayed to determine alterations in exocytosis in a population of cells. When viewed in the FACS, cells have particular characteristics as measured by their forward and 90 degree (side) light scatter properties. These scatter properties represent the size, shape and granule content of the cells. Upon activation of the cells with a pro-exocytic stimulus, both the forward and side scatter properties of the cells changes considerably. These properties account for two parameters to be measured as readout for the exocytic event. These properties change in proportion to the extent of exocytosis of the cells and depend on the time course of the exocytic events as well. Alterations in the intensity of light scattering, or the cell-refractive index indicate alterations in exocytosis either in the same cell at different times..

In reply, this section provides support for only two optical properties i.e., forward and side and for exocytosis phenotype and not any other cell phenotypes, as in claim 37.

4. **Sequencing to identify - page 28, lines 10-12 recites:**

> In a preferred embodiment, the fusion partner is a rescue sequence. A rescue sequence is a sequence which may be used to purify or isolate either the candidate agent or the nucleic acid encoding it.

In reply, not only does this section present a different concept but also it relates to a compound, fusion partner. The claim is to a sequencing steps or procedures by which the presumably isolated and identified agent is sequenced. Because the specification, even the above quoted support, does not disclose a single candidate agent that has been isolated and identified hence, it is not seen how sequencing can occur.

Accordingly, claim 37 in its entirety or the disparate sections cited by applicants do not support the presently amended claims. Claims in its entirety should appear in the specification as in the claim to make clear what applicants are claiming and not picking and choosing disparate elements/ sections in the specification to make up a claim. Cf. with the claims of the parent issued patent US 6,897,031(‘031 Patent) which finds support in its entirety in specification at e.g., col. 2, lines 22-35. Thus, the claim is not supported in the parent application, now the issued ‘031 Patent (Please see

further the indefiniteness rejection under 35 USC 112, 2nd paragraph below).

Written description Rejection-Necessitated by Amendments

Claims 37-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the genus of the invention.

Applicants are not in possession of the claim method in general as recited in claim 37. The specification at the time of filing does not describe a library of 10^3 vector encoding presumably also 10^3 different kinds of candidate agents. It does not describe all or any kinds of vectors, whether of the same or different type that would encode any or all kinds of different agents. There is no description of a candidate agent that has been isolated or identified by the encoded diverse

library of 10^3 vectors that alters a phenotypic change to any population of mammalian cells. Throughout the specification reference is made only to a library of population of 10^3 but not to a 10^3 library vector that encodes (absent any gene or nucleic acid therein) an enormous numbers of different kinds of candidate agents. The specification' working example describes the effect of a single candidate known agent p21 and its phenotypic effect to a population of 10^3 cells. There is no description of how the single known p21 has been selected, purified and identified form the 10^3 library of vectors, itself encoding said agents. Nor is there a description of the candidate agents that alters any or all kinds of phenotypes in a population of cell. Since no identification of a candidate peptide agent has been made and the single protein (not peptide) is known hence, it is not readily apparent how sequencing can be done to an already known protein. There are no characterizing features of the genus candidate agent coupled with a functional limitation or core sequences corresponding with the single protein described in the specification to lead a skilled artisan to the general method.

To satisfy a written description requirement for a claimed genus a sufficient description of a representative number of species by actual reduction to practice or by disclosure of

relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

Enablement Rejection-Necessitated by Amendment

The enabling disclosure provided in the specification is not commensurate in scope with the recited general method. The method employs broadly a huge 10^3 library vectors itself encoding directly any of the different candidate agent that affects any phenotype type of any cell in a population. The specification provides only broad generalized statements. It would take an undue amount of experimentation to determine the 10^3 library of vectors encoding different candidate agents that alters any type of phenotype to any kind of cells in a population. This is made more complex since the specification does not provide support for the claim general method. (Please see the new matter rejection above.)

The factors that are to be considered in the determination of undue experimentation are disclosed in In re Wands, (U.S.P.Q. •2d 1400 (CAFC 1988). These include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the art, and the predictability of the art and the breadth of the claims.

1). The specification fails to give adequate direction and guidance in how to make the 10^3 library of vectors encoding any candidate agent(s). The specification describes only a 10^3 library of cell population. Therefore, the specification does not teach how to go about making a vectors of 10^3 library of different kinds encoding different kinds of candidate agents. The specification does not describe from the 10^3 library the candidate agent that has phenotypically alter a population of cells to enable its isolation, identification and sequencing.

2). Applicants have failed to provide any working examples for a 10^3 library of any kind of vectors, whether the same or of different type encoding an enormous diverse kinds of candidate agents that alter a number of phenotypes of a cell population. The working example provides for a single, known protein p21. It is not apparent from the specification whether

this single, known protein is the one obtained from the encoding library of vectors, isolated from the rest of the cells, identified and sequenced. The specification does not teach the sequence of the p21, and if it is known, the need for its sequencing.

3). The state of the prior art is such that the consequences of some bioactive agent and cell interaction on some cells have not yet been fully determined or elucidated. See Polyak (Genes and Development) at e.g., page 1945, col. 2. 4). The art is inherently unpredictable with respect to the numerous types of agents altering even a single phenotype of a single cell let alone a population of cells. Also, the use of a wide variety of libraries with candidate agent presentations can be displayed in an extraordinarily large number of conformations. See Luo (Nature) e.g., at page 159, col. 2, first incomplete paragraph. Nakanishi (The EMBO Journal) e.g., at page 556, col. 2, last paragraph and Tournier et al (Molecular Biology of the Cell) e.g., at page 658, col. 2. 5). The breadth of the claims encompasses large possible combinations for the different unnamed or undefined variables of library of vectors, candidate agents, phenotypes and cell population.

6). While the level of skill in the art is high, the molecular biology and gene art is so unpredictable that it would require undue experimentation to make the invention commensurate in scope with that claimed in the absence of adequate guidance or direction as set forth above. This is especially true when the present claim is described in general and not supported in particular by the specification. The specification provides only definitions of the terms use in the general method. For example, at page 16, line 8 up to-page 30, line 15 the term "candidate bioactive agent" is defined as any molecule, e.g., protein, small organic molecule, carbohydrates (including polysaccharides), polynucleotide, lipids, etc.

Applicants' disclosure would not enable a skilled artisan to carry out the claimed methods without undue experimentation. The specification does not only provide support for the generic method and only provides definitions for the broad components in the method.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 37 is vague and indefinite as the steps lack nexus. For example, step 2 recites subjecting the population of cells to physiological signal in the absence of the candidate bioactive agents. However, the succeeding steps do not correlate step 2 to the succeeding step of sequencing the nucleic acid encoding the candidate agents i.e., whether a physiological signal is similarly applied in the presence of a candidate agent. This is made more complicated as Step 2 is inconsistent with the teachings in the disclosure. See the new matter rejection above.

2. Claim 37 method is inconsistent with the disclosure method. For example, the specification teaches a library of 10^3 cells not vectors. Furthermore, it is unclear whether the vector itself is encoding the candidate agent, given no support from the specification.

3. There is an inconsistency between the preamble in claim 37 which is drawn to screening (incomplete as to what is being screened) and the body of the claim which recites for identifying the nucleic acid encoding candidate agents. It is vague and indefinite as to whether the method is directed to screening a population of cells that have been phenotypically altered by the candidate agent or the candidate agent itself. This is made more indefinite as the specification does not provide support for the preamble and body of the claims drawn to sequencing.

4. The use of the word 'type' in claim 37 to an otherwise definite expression extends the scope to render it objectionable under 35 U.S.C. § 112, second paragraph." See Ex parte Copenhaver, 109 USPQ 118 (Bd. App. 1955). It is vague and indefinite in what manner the cells are considered of the same "type". Please note that the first step recites mammalian cells. Step 2 recites only cells. It is vague and indefinite as to whether the cells are of the same species encompassed by the broad mammalian cells.

5. Claim 37 recites the limitation "the same type", "in the absence of the candidate bioactive agents", "the individual cells", "the basis of at least three"and"the nucleic acid

encoding". There is insufficient antecedent basis for this limitation in the claim.

6. Claim 37 is vague and indefinite as to the physiological signal the population of cells is subjected thereto given that the cells are grown in vitro(?). Cf. with the specification disclosure above under new matter rejection.

7. Claim 38 is vague and indefinite as to the "other" cells being referred to given no identifying features of one cell to the other. Are the cells of the same or different type(s) in a population? "Sad" in line 1 should be --said--.

8. Claim 40 is vague and indefinite in the recitation of at least one optical property selection when the base claim recites at least three as the minimum.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 37, 40 and 42-43are rejected under 35 U.S.C. 103(a) as being obvious over Uhr et al.

For claims 37, 40 and 42-43; Uhr discloses at e.g., col. 3, line 50 up to col. 4,line 37; a method of identifying a candidate substance, capable of inducing alteration of cellular phenotype comprising contacting the population of cells to be analyzed with a panel of (library of candidate agents) directed against distinct cell surface molecules, under conditions effective to allow antibody binding. The antibodies would be labelled in a manner to allow their subsequent detection, such as by tagging with a fluorescent label. By using fluorochromes that can be excited by 2 different lasers to give off light at 4 different wavelengths (reads on the claim at least 3 optical parameters), it is possible to use 4 distinct antibodies to 4 different surface antigens and, in addition, to use 2 light scattering parameters, direct and orthogonal (reads on claim 40). Thus cells can be separated on the basis of 6 parameters (reads on claim 37). The population of tumor cells with bound antibodies may then be separated by cell sorting, preferably using fluorescence-activated flow cytometry. Uhr discloses that for multiparameter cell sorting, it is contemplated that one

would wish to employ a combination of agents that results in independent signals of 4 different wavelengths. This may be readily achieved by using four distinct monoclonal antibodies. Alternatively, the fourth signal may be supplied by employing a DNA stain which results in color generation, such as Hoechst, and in these circumstances only three monoclonal antibodies may be used in the separation procedure. Uhr further discloses at e.g., cols. 7-14, Table 1 the panel of antibodies. Uhr discloses or suggests at e.g., col. 22, lines 14-20 the preparation of vectors which incorporate nucleic acid sequences capable of encoding the desired genes introduced into the cells to be treated. The replication defective retrovirus (reads on claim 43) may be used, as may other vectors. Fig. 1 discloses that Flow cytometry was performed on a FACS wherein forward light scattering, orthogonal light scattering, FITC and PE signals were determined for 30,000(3 x10^4) cells. FIG. 3 shows cDNA synthesized from a mixture of 10^4 cell-equivalents of total RNA and 10^6 (myc and fos panels) or 10^7 (actin panel). BCL1 cells bear surface immunoglobulin of both the mu/lambda and delta/lambda isotypes that share a common idiotype (Id), as defined serologically and by sequence analysis (Krolick et al., 1979).

Uhr further discloses at e.g., col. 22:

> …… DNA encoding key gene**s** such as, for example, c-fos or c-jun, may be **applied directly to cells, in the form of oligonucleotides, or other genetic constructs…..The preparation of vectors which incorporate nucleic acid sequences capable of encoding the desired genes, once introduced into the cells to be treated, is contemplated.** (Emphasis added).

Uhr, alone, discloses or teaches all the elements of the claim method except the sequencing of the candidate agents. Such sequencing would have been obvious to one having ordinary skill in the art at the time the invention was made given the known structure of antibodies or antigens taught by Uhr.

Claims 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhr in view of Hide.

Uhr is discussed above. Uhr discloses a FACS means of measuring the altered cellular phenotype but not exocytosis induced by Ca++ or ionomycin.

Hide discloses e.g., at page 588, col. 2 that cells contain large numbers of secretory granules which makes them highly refractile as manifested in the light-scattering properties of the cells, particularly at around 90 degrees. When the cells have undergone exocytosis, their refractivity is lost and their

ability to scatter light at 90 degree is correspondingly diminished. This attribute has been used to classify populations of cells. Hide further disclose at e.g., page 592 that a suboptimal concentration of the stimulus ionomycin will distinguish between populations of cells that have differing thresholds to stimulus by intracellular Ca++. The strength of the stimulus selects the cells which then proceed to a full degranulation. It would have been obvious to one having ordinary skill in the art at the time the invention was made to measure the cellular phenotype alteration in the method of Uhr by exocytosis using such stimulus as Ca++ or ionomycin as taught by Hide. Hide teaches that exocytosis measurement when stimulated by Ca++ or ionomycin will distinguish between populations of cells that have differing thresholds. The strength of the stimulus would select the cells which then process to full exocytosis. One would have been motivated to use stimulus as Ca++ or ionomycin to differentiate one cell from another by the effect of the stimulus. One would have a reasonable expectation of success since exocytosis phenotype has been used to differentiate cells in a population using FACS as successfully shown by the works of Hide.

Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uhr in view of Conneally.

Uhr is discussed above. Uhr does not positively teach library of retroviral vectors albeit, at least suggests said library of retroviral vectors. However, Conneally positively teaches at e.g., page 461, under the Discussion heading, the advantages in the use of recombinant retroviuses for the genetic modification of cells. One of the advantages is the ability to assess gene transfer to specific subpopulations of cells immediately after infection. The detectable level is sorted by FACS. The use of recombinant retroviral vectors to transfect cells would have been obvious to one having ordinary skill in the art at the time the invention was made as taught by Conneally and at least contemplated by Uhr. The advantages provided by Conneally above would provide the motivation to use this recombinant virus. One having ordinary skill in the art would have a reasonable expectation of success in using retroviral vectors. These vectors have been conventionally use in the art and has been successfully employ in the art as taught by Conneally and at least suggested by Uhr, especially in transfecting mammalian cells.

Response to Arguments

Applicants argue that Uhr is deficient because a) Uhr does not teach the use of a library of at least 10^3 vectors encoding different candidate agents, as required by the rejected claims. Uhr describes the use of a vector that encodes c-jun or c-fos into cells to induce cell cycle arrest. Thus, at best, Uhr suggests a method that employs one of two vectors (which encode c-jun or c-fos). Based on Uhr's disclosure, there would be no reason to use more than two different vectors, let alone at least 1,000 vectors as required by the rejected claims.

In reply, attention is drawn to FIG. 3 which shows cDNA synthesized from a mixture of 10^4 cell-equivalents of total RNA and 10^6 (myc and fos panels) (which reads on a library).

Uhr further discloses at e.g., col. 22:

> …… DNA encoding key gene**s** such as, for example, c-fos or c-jun, may be **applied directly to cells, in the form of oligonucleotides, or other genetic constructs…..The preparation of vectors which incorporate nucleic acid sequences capable of encoding the desired genes, once introduced into the cells to be treated, is contemplated.** (Emphasis added).

b) Applicants argue that Uhr does not introduce candidate agents into cells and subject the cells to a physiological signal as separate events, as required by the rejected claims. But recognize that Uhr merely introduces compounds (c-jun or c-

fos) into cells to induce cell cycle arrest. At best, the compounds can either be considered candidate agents (in which case there is no separate physiological stimulus) or as physiological stimuli (in which case there is no candidate agent). Either way, introducing candidate agents into cells and subjecting the cells to a physiological signal as separate events is not disclosed by Uhr.

In reply, the claims do not recite that the candidate agents introduced into cells are subjected to a physiological signal as separate events. Read in the light of the specification disclosure, the two separate events did not occur as such. Please see the 35 USC 112(new matter) and 2nd paragraph rejections above.) When read in light of the disclosure teachings, Uhr similarly measures or evaluates cell-cell or antigen-antibody interaction, inter alia, that is included in the broad scope of the claim physiological signal.

c) Applicants argue that Uhr does not disclose using FACS to examine the individual cells in the cell population that has been grown in vitro.

In reply, Uhr discloses at e.g., Example IV:

> To allow the more rapid development of further work, the inventors have established a BCL.sub.1 line, 3B3, that replicates every three days in vitro …. The 3B3 in vitro cell line will be especially useful for investigating the kinetics of gene induction following anti-Ig treatment, and will facilitate the introduction of DNA constructs, by transfection and subsequent selection, to investigate the role of oncogene expression in dormancy induction.

d) Applicants argue that Uhr does not disclose sequencing the nucleic acid encoding the candidate agent in a cell that has an altered phenotype. Since the identities of Uhr' s clones (which, at best would encode c-jun or c-fos) would be known before any experiments were initiated, there would be no need for this step to be performed.

In reply, Uhr further discloses at e.g., col. 22:

> …… DNA encoding key gene**s** such as, for example, c-fos or c-jun, may be **applied directly to cells, in the form of oligonucleotides, or other genetic constructs…..The preparation of vectors which incorporate nucleic acid sequences capable of encoding the desired genes, once introduced into the cells to be treated, is contemplated.** (Emphasis added).

Furthermore Uhr discloses at e.g., Fig. 3:

> BCL1 cells bear surface immunoglobulin of both the mu/lambda and delta/lambda isotypes that share a common idiotype (Id), as defined serologically and by sequence analysis (Krolick et al., 1979).

Read in light of the specification, the disclosure does not define any sequencing step or any candidate agent that has been identified such that sequencing is done. Applicants' cite page 28, lines 10-12 which states:

> In a preferred embodiment, the fusion partner is a rescue sequence. A rescue sequence is a sequence which may be used to purify or isolate either the candidate agent or the nucleic acid encoding it.

This is not a sequencing step rather an unidentified candidate agent fused only to a rescue sequence only known by its definition but also of no known sequence. The Examples in the specification also uses known candidate agents and does not teach an isolated and identified candidate agent that has been sequenced.

Claims 37 and 40-44 are rejected under 35 U.S.C. 103(a) as being obvious over Nolan in view of Jia-ping and Uhr et al for reasons of record as reiterated below and Board's decision mailed on 7/21/10.

Nolan et al discloses at e.g., page 31, line 1 up to page 32, line 6 a method comprising introducing a molecular library of randomized candidate nucleic acids into a plurality of cells, a cellular library. Each of the nucleic acids comprises a different, generally randomized, nucleotide sequence. The

plurality of cells is then screened for a cell exhibiting an altered phenotype. The altered phenotype is due to the presence of a transdominant bioactive agent. Any phenotypic change may be observed, detected, or measured on the basis of the screening methods. Suitable phenotypic changes include, but are not limited to gross physical changes such as changes in cell morphology, cell growth (cell cycle, as claim), cell viability (apoptosis, as claim), changes in the expression of one or more RNAs, proteins, changes in the localization of one or more RNAs, proteins, changes in the bioactivity or specific activity of one or more RNAs, proteins, changes in the secretion of ions, cytokines, hormones, growth factors, or other molecules and etc. (reads on the claim physiological signal). The altered phenotype is detected in a wide variety of ways and will generally depend and correspond to the phenotype that is being changed. Generally, the changed phenotype is detected using, for example, Standard cell viability assays, including both increased cell death and increased cell viability, for example, cells that are now resistant to cell death via virus, bacteria, or bacterial or synthetic toxins; standard labeling assays such as fluorometric indicator assays for the presence or level of a particular cell or molecule, including FACS or other dye staining techniques; biochemical detection of the expression of target compounds

after killing the cells. Once a cell with an altered phenotype is detected, the cell is isolated from the plurality which does not have altered phenotypes. This may be done in any number of ways, as is known in the art, and will in some instances depend on the assay or screen. Suitable isolation techniques include, but are not limited to, FACS or other cell vitality indicator dyes.

Nolan does not disclose a method in which the cellular phenotype is exocytosis and at least 3 optical parameter cell sorting by FACS (although suggests said FACS analysis). However, Jia-ping discloses a method of sorting cells by multi-parameter sorting technique using flow cytometer including exocytosis. The method provides for an increased of purity of the divided cell and further information of the different cell subpopulations (page I).

Uhr is discussed above. It would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the changes in the exocytosis phenotype of a cell by at least 3 optical parameters in the method of Nolan in the manner as taught by Jia-ping and Uhr. One having ordinary skill in the art would have been motivated to sort the alteration in the phenotypic cells by at least 3 parameters based on exocytosis phenotype of the cell for the advantages

taught by Jia-ping and Uhr. The alteration in the exocytosis phenotype of the cell provides further information of the different cell subpopulations such that an increased purity of the divided cell is obtained.

Claims 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan in view of Jia-ping and Uhr et al as applied to claims 37 and 40-44 above, and further in view of Hide et al.

Nolan is discussed above. Nolan discloses a FACS means of measuring the altered cellular phenotype but not exocytosis induced by Ca++ or ionomycin.

Hide discloses e.g., at page 588, col. 2 that cells contain large numbers of secretory granules which makes them highly refractile as manifested in the light-scattering properties of the cells, particularly at around 90 degrees. When the cells have undergone exocytosis, their refractivity is lost and their ability to scatter light at 90 degree is correspondingly diminished. This attribute has been used to classify populations of cells. Hide further discloses at e.g., page 592 that a suboptimal concentration of the stimulus ionomycin will distinguish between populations of cells that have differing thresholds to stimulus intracellular Ca++. The strength of the

stimulus selects the cells which then proceed to a full degranulation. It would have been obvious to one having ordinary skill in the art at the time the invention was made to measure the cellular phenotype alteration in the method of Nolan by exocytosis using such stimulus as Ca++ or ionomycin as taught by Hide. Hide teaches that exocytosis measurement when stimulated by Ca or ionomycin will distinguish between populations of cells that have differing thresholds. The strength of the stimulus would select the cells which then process to full exocytosis. One would have been motivated to use stimulus as Ca++ or ionomycin to differentiate one cell from another by the effect of the stimulus. One would have a reasonable expectation of success since exocytosis phenotype has been used to differentiate cells in a population using FACS.

Response to Arguments

Applicants assert that the issue resolved in appeal was whether the instant application was entitled to claim priority to parent application serial no. 09/062,330, now issued as U.S. patent 6,897,031, for claims that recited "at least five" FACS parameters. New claim 37 recites "at least three" parameters, explicit support for which is found in both the instant application (e.g., at page 4, line 3) and the parent application

(e.g., at page 3, line 12). Likewise, support for the remainder of the elements of the instant claims is found in the parent application (see table above). A Declaration under 35 U.S.C. § 1.131 (the "Fisher declaration"; attached as Exhibit A) was previously submitted with the Applicants' response of July 24, 2006, in order to obviate a rejection over a near identical combination of references (i.e., Nolan in view of Jai-ping or Ryan). The Fisher Declaration established invention of the subject matter of the rejected claims prior to the Nolan's publication date. The Applicants' prior arguments were deemed unpersuasive by the Board solely because the parent application allegedly does not support claims that recited "at least five" FACS parameters. Because the new claims recite "at least three" parameters (an element that is explicitly supported in the instant application and the parent application; see above), the priority claim of the instant application is proper, and the Fisher Declaration is believed to show prior conception of the claimed invention prior to Nolan's publication date. Thus, Nolan cannot preclude the patentability of the rejected claims. The Examiner is respectfully requested to review the arguments set forth on pages 9-11 of the Applicants' response of July 24, 2006, in the context of the new claims, and withdraw this rejection. Withdrawal of this rejection is requested. With the

above in mind, the Applicants note that MPEP §§ 715.02~ and 715.032 explicitly state that a showing of completion of a single species encompassed by a genus claim is sufficient to antedate a reference. As such, according to the MPEP, the Fisher Declaration need not show completion of every species within the claimed genus for this rejection to be withdrawn. To the extent that any further discussion is necessary, the Examiner is referred to the Applicants' response of February 24, 2006.

In reply, the Board's decision at pages 12 -14 states:

14. The filing date of the instant application is April 16, 1999 (see Transmittal of New Application (entered April 16, 1999)), which is more than one year after the publication date of the Nolan reference.

15. The Specification states that "[t]his application is a continuation-in- part of U.S. Application Serial No. 09/062,330, filed on April 17, 1998 [now U.S. Patent No. 6,897,031 B1], and U.S. Application Serial No. 09/157,748, filed on September 21, 1998 (Specification 1 (as amended September 24, 2004)).

16. Thus, to remove the statutory bar set by 35 U.S.C. § 102(b) against patenting claims anticipated or obviated by printed publications available more than one year prior to an application's filing date, Appellants' claimed subject matter must find support in Application Serial No. 09/062,330(‘330

application), filed on April 17, 1998, which issued as U.S. Patent No. 6,897,031 B1.

17. The Examiner finds: The 09/062330 (now US Patent 6,897,031) ('031 Patent) does not provide support for now newly presented claim 37 in its entirety (cf. with the ‘330 application and remainder of the claims as given in the new matter rejection above. For example, the new claim to a “library of at least 10^3 vectors encoding different candidate agents”; ‘subjecting the population of cells to a physiological signal that stimulates a phenotype in cells of the same type in the absence of the candidate bioactive agents”; "at least 3 optical properties" as applied to the different claim cellular phenotypes and “sequencing of the nucleic acid encoding said candidate agent”.

The '031 patent states:

> Described is a method for screening for alterations in exocytosis of a population of cells. The cells are sorted by a FACS machine by assaying for alterations in at least three of the properties selected from the group consisting of light scattering, fluorescent dye uptake, fluorescent dye release, annexin granule binding, surface granule enzyme activity, and the quantity of granule specific proteins. Methods for screening for bioactive agents capable of modulating exocytosis in a cell are also described. The methods provide for reduced background and increased specificity without increasing the time or steps involved in assaying for exocytosis. ('031 patent, abstract).

We agree with the examiner that appellants have not shown that the Nolan reference is unavailable as prior art against the presently rejected new claims. As noted above, Appellants cannot avail themselves of an antedating declaration under 37 C.F.R. § 1.131 if the rejection is a statutory bar. See In re Foster, 343 F.2d at 989-90. Thus, to avoid the statutory bar set by 35 U.S.C. § 102(b), Appellants must find descriptive support for the rejected claims in a priority application filed less than one year after publication of the Nolan reference. In the instant case, only the '330 application, which issued as the '031 patent, and which is asserted as a continuation-in-part parent to this application, has such a filing date (see FF 15). Applicants are also directed to the further responses of February 24, 2006, as relied upon by applicants above.

Thus, the Fisher declaration under 35 U.S.C. § 1.131 does not overcome the 35 USC 103 rejection as the declaration has no effect on a 35 USC 103 based on 35 USC 102(b) rejection for the reasons provided by the Board in their decision and the above rejections.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1639